Author's response to reviews

Title: A Six-generation Chinese Family in Haplogroup B4C1C Exhibits High Penetrance of 1555A>G-induced Hearing Loss

Authors:

Yan Bai (baiyan1995@sina.com)
Zheng-min Wang (fjswzm@gmail.com)
Wenjia Dai (daiwenjia@126.com)
Qing-zhong Li (ligingzhong@163.com)
Guo-ling Chen (elebell@163.com)
Ning Cong (congningen@yahoo.com.cn)
Min-xin Guan (gminxin88@gmail.com)
Huawei Li (hwli@shmu.edu.cn)

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Author's response to reviews: see over
Dear Editor:

Thank you for your kind letter of my manuscript (MS: 1889349189388859 - A Six-generation Chinese Family in Haplogroup B4C1C Exhibits High Penetrance of 1555A >G-induced Hearing Loss) on 2 Aug 2010. We revised the manuscript in accordance with the reviewers’ comments. Here below is our description on revision according to the reviewers’ comments.

Answers to reviewer Regie Santos-Cortez:

Major compulsory revision:

1. Your covariance analysis reportedly showed that m.1555A>G and aminoglycoside exposure are main influence factors, but this is not included in the manuscript and was not considered as basis for your conclusion. Because it is hard to establish genotype-phenotype correlation based on severity for mitochondrial disorders, it is possible that presence of the m.1555A>G places the individual at risk for hearing loss, but the severity of the disease is based on the interplay of mutation with other factors such as age and aminoglycoside exposure.

Reply:
The 1555A>G mutation is the most common cause of aminoglycoside-induced and non-syndromic deafness. As reviewer said that presence of the m.1555A>G places the individual at risk for hearing loss. The individual who carry this mutation will be deafness when they had normal or even very small dosage aminoglycoside injection. Because the m1555A>G mutation leads to sensitivity to aminoglycosides. This conclusion was demonstrated in many studies. So this is not included in our manuscript. We added this in the revised manuscript. On the other hand, the patients carrying the A1555G mutation can also suffer hearing loss without any aminoglycosides exposure. So the severity of the disease is based on the interplay of mutation with other factors such as nuclear genes and
aminoglycoside exposure.

2. The conclusion states that nuclear genes (GJB2) and aminoglycosides are responsible for hearing loss in your pedigree, however based on Table 1 only 8/21 individuals with hearing impairment have aminoglycoside exposure, while 8/21 individuals with hearing impairment have GJB2 variants. Note also that all the GJB2 variants in this family were previously documented as benign. On the other hand, all hearing-impaired individuals are m.1555A>G carriers, although 3 hearing individuals are also carriers.

Reply:

The 1555A>G mutation can lead non-syndromic deafness. The patients carrying the A1555G mutation can also suffer hearing loss without any aminoglycosides exposure. Our noted that the individual who carried the 1555A>G mutation and T123N in nuclear genes (GJB2) may be more severe hearing loss in this pedigree. Through literature review, we found T123N was an unclassified mutation in GJB2 in Asian population. Due to its coexistence with 1555 A> G mutation in 6 affected subjects in our pedigree, we just suspected that the heterozygous T123N may be relevant of the phenotype expression and penetrance of hearing loss in this pedigree. We had revised it in manuscript.

3. If you have information on prevalence of presbycusis and average thresholds by age in your study population, this would help to determine whether the hearing loss in the third generation is more due to age rather than m.1555A>G. Data for presbycusis thresholds from other populations can also be derived. Because age is not included in Table 1, it is hard to determine if the fourth generation would not be affected by presbycusis and so the aminoglycoside exposure and possibly the m.1555A>G variant are stronger predictors of hearing loss. Can it also be possible that the third generation was also exposed to aminoglycosides, but they just did not know or have a poor recollection of it because it happened much farther back in time? I therefore maintain that your article would highly benefit by the inclusion of statistical evidence
of the contribution of the different factors that were phenotyped in this pedigree to the presence and degree of hearing impairment. I am particularly impressed by the amount of phenotyping work you have done, thus I propose that additional statistical work is performed so that more people can benefit from your work. The conclusion should then be rephrased

Reply:
The age of all the members of this pedigree were added into the revised manuscript. I think it will be clear that no one individual in the fourth generation will more than 50 years old. So the aminoglycoside and m1555A>G were the main factors of high penetrance and deafness.

Hearing loss of presbycusis was defined based on two averages of hearing thresholds: 500, 1,000, and 2,000 Hz greater than 25-decibel (dB) hearing level (HL) (hearing loss); and 2,000, 4,000, and 8,000 Hz greater than 40-dB HL (high-frequency hearing loss). In U.S. studies, prevalence estimates of hearing loss at birth are approximately 0.5%, and in children, approximately 5%. In adults aged 65 and older, prevalence estimates range from 30% to 83%. We failed to found average thresholds by age in our study population. I can provide details information of the third generation about hearing thresholds.

Minor revisions:
Please correct the GJB2 variant I203T in Table 1.
Pedigree drawing, figure 2 and table 1 can be improved with better resolution.

Replay:
We had corrected the GJB2 variant I203T in Table 1 and improved the resolution of Pedigree drawing, figure 2 and table 1

A revised manuscript with the correction sections red marked was attached as the supplemental material and for easy check/editing purpose.

We acknowledge the reviewer’s comments and suggestions very much, which are
valuable in improving the quality of our manuscript. Should you have any questions, please contact us without hesitate.

Yours sincerely,

Huawei Li